Development and Characterization of an Isolated and Perfused Tumor and Skin Preparation for Evaluation of Drug Disposition

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ABSTRACT

The purpose of this study was to develop a model in which the regional pharmacokinetics of a drug in tumor and nontumorous tissue could be evaluated under a variety of physiological conditions. To this effect, the growth of a human choriocarcinoma cell line (JAR) was evaluated in pigs immunosuppressed with 25 mg cyclosporine/kg every 24 h. During an initial study, we demonstrated that suspensions containing approximately 3 million JAR cells with and without 1 million normal human fibroblasts injected s.c. into the inguinal region of pigs resulted in the growth of tumors consisting primarily of polygonal neoplastic cells. Multinucleate tumor cells, inflammatory cells, necrotic debris, and vascular endothelial cells were also present. Maximal tumor size was noted on day 12, after which time tumor regression occurred. The coinoculation of fibroblasts resulted in significantly larger tumors. Two single pedicle, axial pattern tubed flaps were created in the inguinal area of 4 pigs. JAR cells and fibroblasts were transplanted to one flap to allow for tumor formation. The other flap served as a nontumorous control. Both flaps were removed for perfusion with a physiological solution 11 days later. Glucose utilization, lactate concentrations, lactate dehydrogenase activities, and microscopic evaluation of skin samples were used to assess flap viability. All flaps remained viable for 8 h of perfusion. The only differences detected between nontumorous and tumor flaps was the initial perfusion pressure which was significantly lower in tumor flaps ($P < 0.05$). The isolated perfused tumor and skin flap is unique in that it consists of a tumor surrounded by normal tissue with an intact microvascular system and can be utilized to design regional pharmacokinetic studies describing drug distribution in tumor tissue.

INTRODUCTION

Pharmacokinetic studies are essential to evaluate physiological and pharmacological factors that might influence drug concentrations in tumors and critical normal tissue. However, the ability to predict drug flux in a region from data obtained during systemic pharmacokinetic analysis is limited. Drug concentrations within a tumor are a function of the uptake of drug from afferent blood and the elution of drug into efferent blood (1). Since the uptake and elution of drug varies between regions, systemic blood concentrations are not always proportional to tissue concentrations and may not reveal some important aspects of drug disposition (2, 3). Few organs or tissues provide access to both venous and arterial blood, making regional blood sampling problematic (1). In addition, the inability to independently control local tissue factors (e.g., pH, temperature, disease states, blood flow) without producing serious systemic consequences makes one unable to use data obtained from systemic pharmacokinetic studies to clearly define the extent to which these factors may affect drug disposition. The failure of a physiological pharmacokinetic model to completely describe the rate of loss of cis-diaminedichloroplatinum (cisplatin) from the tumor compartment and the wide variability of tumor drug concentrations reported in other in vivo studies emphasize these points (4–7).

Cell culture systems and multicellular spheroids are required to define mechanisms of drug activity on selected cell populations. However, neither system is capable of responding to physiological alterations or developing the complex microenvironmental conditions seen in vivo (1, 8). It is difficult to extrapolate data from these systems to generate clinically meaningful systemic pharmacokinetic strategies. An intermediate model is needed to expedite the evaluation of alternate strategies for chemotherapeutic agent delivery.

The IPPSF is an anatomically and physiologically intact, viable, isolated and perfused tubed skin preparation which has been used extensively to study cutaneous function and topical drug absorption (9). The IPPSF is maintained in a well controlled environment allowing for the effects of altered physiological or perfusate parameters and the coadministration of drugs to be quantitated. The intact microcirculation, which is responsive to pharmacological manipulation, permits monitoring of arterial and venous perfusate concentrations over time yielding construction of relatively simple pharmacokinetic models of drug distribution and binding. The IPPSF is ideally suited for detailed pharmacokinetic studies, the results of which are easily extrapolated to in vivo systems. A mathematically identifiable physiological pharmacokinetic model of cutaneous drug distribution in the IPPSF, which quantitates experimental data, has been defined (10). This model was accurate to within 0.1% in predicting the disposition of unbound cis-diaminedichloroplatinum and diammine (1, 1-cyclobutane-dicarboxylato) platinum (carboplatin) in the IPPSF.

We have utilized the IPPSF to develop a model in which the regional pharmacokinetics of a drug in a tumor can be evaluated under defined physiological conditions. Tumor cells are transplanted to and grown in a skin flap. The flap, incorporating the tumor and surrounding tissue, is then isolated and perfused with a physiological solution. Arterial influx and venous efflux profiles of specific chemotherapeutic agents can be studied to develop regional pharmacokinetic models and define drug disposition parameters for both the tumor and normal tissue. Specific physiological variables can be manipulated, thereby determining their effects on drug uptake.

MATERIALS AND METHODS

Animals and Cyclosporine Protocol. Eleven weanling Yorkshire pigs, weighing approximately 15 kg (range, 9–19 kg) were used for this study. Pigs were given cyclosporine at 25 mg/kg every 24 h p.o. for at least 7 days prior to transplantation of cells and continued until harvesting of tumors or flaps. This dose was based upon the results of a previous study evaluating the pharmacokinetics, inhibition of lymphoblast transformation, and toxicity of cyclosporine in pigs (11). Blood samples were collected into EDTA 24 h after cyclosporine administration at least once during the treatment period. Trough cyclosporine concentrations were determined to ensure that they were above those previously reported to be immunosuppressive in pigs. A commercially available radioimmunoassay kit (Sandimmune Monoclonal; Incstar Corp., Stillwater, MN) was used to measure concentrations of the parent compound.

1 The abbreviations used are: IPPSF, isolated perfused porcine skin flap; IPTSF, isolated perfused tumor and skin flap; NHF, normal human fibroblasts.
During the initial growth and reproducibility studies, pigs were sedated with ketamine hydrochloride and xylazine hydrochloride. Pigs were premedicated with xylazine hydrochloride and ketamine hydrochloride and maintained with halothane anesthesia during surgical procedures.

Tumor Implantation. The use of a human choriocarcinoma cell line (JAR) was determined to be suitable for growth in pigs during a pilot study in which the growth of tumors following transplantation of UM-UC-9, HXG-2, and JAR cells was evaluated. A beneficial effect of the concurrent inoculation of fibroblasts on the growth of human tumor xenografts has been demonstrated previously (12, 13). We also evaluated the effect of fibroblasts on tumor growth. JAR cells and NHF were grown as monolayers in Dulbecco's modified essential medium with 10% serum and 5 ug/ml insulin under standard incubation conditions (37°C and humidified 5% CO2:95% air).

Immediately prior to transplantation, cells were harvested by trypsinization, quenched with serum-containing culture media, and pelleted by centrifugation at 1500 rpm for 3 min. Cell pellets were resuspended in 1.5 ml Dulbecco's phosphate buffered saline. During an initial growth study, suspensions containing approximately 3 million JAR cells with and without 1 million NHF were injected in duplicate s.c. into 4 designated sites in the caudal inguinal area of one pig. Tumors were excised on day 13 for histopathological examination and morphometric analysis.

To evaluate the serial growth and reproducibility of tumor formation, transplantations were performed in 6 pigs as described previously. The dimensions of the tumor were measured regularly after cell implantation. Tumor volume was calculated as using the formula:

\[ V = \frac{D_1 \times D_2 \times D_3 \times \pi}{6} \]

where \( D_1, D_2, \) and \( D_3 \) are three orthogonal diameters of the tumor. Tissue at the site of tumor formation was excised 24 days after injection for histopathological examination.

Formation and Perfusion of the IPTSF. Skin flaps were created and harvested in 4 pigs according to surgical procedures described previously (9). Briefly, two 12- x 4-cm skin regions perfused primarily by the caudal superficial epigastric arteries and associated paired venae comitantes were marked and incised. Two single pedicle, axial pattern tubed flaps were then created that encompassed these areas. A cell suspension containing 3 million JAR cells with and without 1 million NHF were implanted into the midsection of one flap. The other flap served as a nonneoplastic control. A second surgical procedure was performed 11 days later to cannulate the caudal superficial epigastric artery and harvest each of the flaps.

Each isolated flap was immediately transferred to a perfusion apparatus enclosed in a Plexiglas chamber (Fig. 1). Recirculating medium consisted of a Krebs-Ringer bicarbonate buffer, glucose, bovine serum albumin, amikacin (0.03 mg/ml), penicillin G (10 IU/ml), and heparin (5 USP/ml). The medium was gassed with 95% oxygen:5% carbon dioxide. The pH of the media was maintained at 7.43 ± 0.02 (SE) by the addition of 0.5% hydrochloric acid or 1.0% sodium hydroxide as needed. Concentrated dextrose (45 mg/ml) was infused to maintain perfusate glucose concentrations between 90 and 120 mg/dl. The temperature was maintained at 38.0 ± 0.93°C; the relative humidity was 59.2 ± 8.4%. A mean infusion pressure of 33.5 ± 19.2 mm Hg was applied during perfusion to maintain a flow rate of 1.08 ± 0.10 ml/min.

Arterial and venous samples were collected 30 min after initiating perfusion and then hourly for a total of 8 h for determinations of glucose and lactate concentrations and lactate dehydrogenase activities. Sections of skin and tumor were taken at each time point for each experiment. Glucose utilization (mg/h/g) and differential lactate (mg/h/g) represent the products of glucose extraction (mg/dl) or lactate production (mg/dl), respectively, and the flow rate (dl/h) at each observation time divided by the initial flap weight (g). Glucose utilization, lactate concentrations, lactate dehydrogenase activities, and light microscopic evaluation of skin samples were used to assess flap viabilty.

Histopathological Examination. Tumor samples were placed in 10% neutral buffered formalin and skin samples were placed in half-strength Karnovsky's fixative for at least 24 h. Paraffin embedded tissues were sectioned at 6 μm for light microscopic evaluation. Hematoxylin and eosin stained sections of tumors were examined for tumor presence, cellular morphology, and the extent of lymphocytic infiltration, vascularization, and necrosis. The extent of vascularization was also evaluated in sections stained with Factor VIII related antigen.

Morphometric analysis was performed on tumors harvested during the initial growth study. A 10- x 10-point square ocular grid was used to perform simple point based counting of tumor sections examined at x200. Five hundred points were counted in each of 3 sections from the 4 tumors. Points were counted in microscopic fields that were randomly selected within the outer fibrous capsule. Data were expressed as the percentage of points that consisted of neoplastic cells, inflammatory cells, necrotic debris, vascular endothelial cells, or miscellaneous cells.

Statistical Analysis. Statistically significant differences between means of independent categorical data were determined using Student's t test.

RESULTS

Growth and Reproducibility of Tumors. The mean whole blood cyclosporine trough concentration for all pigs was 668 ± 292 ng/ml (SD). Tumors formed at all transplantation sites. The mean volumes for tumors resulting after the transplantation of JAR cells and JAR cells with NHF was 2.2 ± 0.2 cm (3) (SD) and 3.71 ± 1.1 cm (3), respectively. Results of morphometric analysis are shown in Table 1.

The tumor growth curves are shown in Fig. 2. While all tumors were measurable by day 6, maximal tumor volume was not reached until day 12, after which time tumors began to regress. By day 24 the mean tumor volume was 14% of that present on day 12. Tumors that developed after the transplantation of JAR cells and NHF were significantly larger than those developing after the injection of JAR cells alone (P < 0.05).

Histopathological Examination. Tumors collected during the initial growth study and from skin flaps before and after perfusion were similar in appearance. The tumors formed well-demarcated, sometimes lobulated, s.c nodules, consisting primarily of sheets and cords of polygonal neoplastic cells (Figs. 3 and 4). Neoplastic cells were pleomorphic, with abundant pale amphophilic cytoplasm and oval to irregular, vesicular nuclei containing 1-3 prominent nucleoli. Multinucleate tumor cells containing up to 10 nuclei were common. Mitoses were numerous. Tumors were supported by a fine fibrovascular stroma and surrounded at their periphery by a narrow zone of fibroblasts. There was infiltration of all tumors by lymphocytes, macrophages, and multinucleate giant cells with fewer neutrophils, plasma cells, and eosinophils. Lymphocytes in particular aggregated focally within the tumors and in a zone at the periphery of the tumors. Random, focal necrosis was present in all tumors. For the initial growth study, the percentages of the total tumor area occupied by
Table 1. Morphometric analysis of tumors

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>JAR</th>
<th>JAR + NHF</th>
</tr>
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</table>
| Neoplastic cells (%)          | 54.6 ± 3.1
| Inflammatory cells (%)        | 23.3 ± 2.7
| Necrotic debris (%)           | 18.1 ± 4.3
| Vascular endothelial cells (%)| 12.2 ± 1.1
| Miscellaneous (%)             | 1.2 ± 0.9 |

Data represent the mean ± SD percentage of 500 points of a 10- × 10-square ocular grid occupied by the cell types listed above. Points were counted in each of 3 sections from tumors removed 13 days after the injection of JAR cells only (n = 2) or the coinjection of JAR cells and normal human fibroblasts (n = 2).

\( ^{a} \) Data represent the mean ± SD percentage of 500 points of a 10- × 10-square ocular grid occupied by the cell types listed above. Points were counted in each of 3 sections from tumors removed 13 days after the injection of JAR cells only (n = 2) or the coinjection of JAR cells and normal human fibroblasts (n = 2).

\( ^{b} \) P < 0.05.

Fig. 2. Mean (± SE) tumor volume plotted against days. Solid line, JAR + NHF; broken lines, JAR only; asterisks, P < 0.05.

Tumor and skin flap model of drug disposition

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The JAR cell line was selected for use in this system based on the results of pilot study in which the growth of human bladder carcinoma (UM-UC-9) and melanoma (HXG-2) cell lines was also evaluated. Tumors resulting after the transplantation of JAR cells were larger and had less associated inflammation than tumors from the other cell lines. The histopathological description of these tumors is similar to what is observed in spontaneous tumors developing in immunodeficient animals. However, we believe that this model system can be used to optimize localized cancer chemotherapy. Perfusion strategies would then be designed for the administration of these chemotherapy agents in whole animal systems. Although not specifically developed for pharmacokinetic experimentation, an isolated perfused tumor model has been developed by implanting Morris hepatomas in the inguinal regions of rats such that they developed an isolated blood supply (23). The IPTSF differs from the Morris hepatoma model in that it may allow for the determination of factors which affect preferential uptake of drugs into tumor versus normal tissue.

Some of the disadvantages that are characteristic of other artificially perfused regions are also present in this system. The system is not under normal hormonal and nervous control (1). The IPTSF does not have a normal lymphatic system. This may contribute to the development of intracellular edema during perfusion and possibly reduce the clearance of highly lipophilic drugs. Conversely, high interstitial fluid pressures may result in reduced intratumoral drug concentrations. The inflammation present in the tumor xenograft, although mild, may also have untoward effects on drug uptake. This model also has limitations common to all xenograft models in that implanted tumors developing in immunodeficient animals have a blood supply and an architectural pattern that is different from those of spontaneous neoplasms. Likewise, normal immune function cannot be assumed which may alter the biological behavior of xenografted neoplasms. However, we believe that this model system can be used to identify strategies that will enhance uptake of drug into the tumor. Further studies to confirm the relationship of the IPTSF to a whole pig-tumor model are under way.

In conclusion, we have created an isolated perfusion system which consists of tumor surrounded by normal tissue with an intact microvascular system. The disposition of specific chemotherapeutic agents in whole animal systems. Although not specifically developed for pharmacokinetic experimentation, an isolated perfused tumor model has been developed by implanting Morris hepatomas in the inguinal regions of rats such that they developed an isolated blood supply (23). The IPTSF differs from the Morris hepatoma model in that it may allow for the determination of factors which affect preferential uptake of drugs into tumor versus normal tissue.

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agents in this model must be evaluated. If factors which favor preferential uptake of drug into tumor versus normal tissue could be identified, further investigation into the possibility of enhancing the therapeutic advantage of regional chemotherapy with these factors would seem justified.

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